Clinical Impact of Chronic Venous Changes Induced by Central Lines in Children: A Cohort with Abnormal Venograms

Gnannt, Ralph ; Chamlati, Racha ; Waespe, Nicolas ; Amirabadi, Afsaneh ; Donnellan, John ; Amaral, Joao ; Parra, Dimitri ; Brandão, Leonardo R ; Connolly, Bairbre

Abstract: PURPOSE To explore the hypothesis that central venous stenosis/obstructions (CVS/O) in children are influenced by prior central venous access devices (CVADs) and are associated with future risk for thromboses. MATERIAL AND METHODS A convenience sample of 100 patients with abnormal venography (stenosis, collaterals, occlusions) documented during peripherally inserted central catheter (PICC) placements were identified from consecutive PICC placements (January 2008 to November 2012). The patients (41 males, 59 females, median age 2.7 years, median weight 11 kg) were categorized based on venographic presence (Group A, n = 53) or absence (Group B, n = 47) of visible connection to the superior vena cava. Each patient's CVAD history, before and after venography, was analyzed (until October 2016). RESULTS Before venogram, Group B patients were associated with a higher number of previous CVADs, larger diameter devices, greater incidence of malposition, and more use of polyurethane catheters than Group A patients ($P < .001$). An ipsilateral PICC was successfully placed in 98% of Group A, compared to 32% of Group B ($P < .001$). After venogram, significantly more Doppler ultrasounds (DUS) were performed and thromboses diagnosed in Group B (57% and 36%) compared to Group A (21% and 8%) ($P < .003$; $P = .001$), respectively. CONCLUSIONS Previous catheter characteristics influenced the severity of venographic changes of CVS/O (Group B). Group B was associated with more subsequent symptomatic thromboses. This information may assist parents and referring physicians to anticipate potential adverse sequelae from CVS/O on the child's venous health.

DOI: https://doi.org/10.1016/j.jvir.2018.08.034

DOI: https://doi.org/10.1016/j.jvir.2018.08.034

CLINICAL STUDY

Clinical Impact of Chronic Venous Changes Induced by Central Lines in Children: A Cohort with Abnormal Venograms

Ralph Gnannt, MD, Racha Chamlati, MD, Nicolas Waespe, MD, Afsaneh Amirabadi, PhD, John Donnellan, MB, Joao Amaral, MD, Dimitri Parra, MD, Leonardo R. Brandão, MD, MSc, and Bairbre Connolly, MB

ABSTRACT

Purpose: To explore the hypothesis that central venous stenosis/obstructions (CVS/O) in children are influenced by prior central venous access devices (CVADs) and are associated with future risk for thromboses.

Material and Methods: A convenience sample of 100 patients with abnormal venography (stenosis, collaterals, occlusions) documented during peripherally inserted central catheter (PICC) placements were identified from consecutive PICC placements (January 2008 to November 2012). The patients (41 males, 59 females, median age 2.7 years, median weight 11 kg) were categorized based on venographic presence (Group A, n = 53) or absence (Group B, n = 47) of visible connection to the superior vena cava. Each patient's CVAD history, before and after venography, was analyzed (until October 2016).

Results: Before venogram, Group B patients were associated with a higher number of previous CVADs, larger diameter devices, greater incidence of malposition, and more use of polyurethane catheters than Group A patients ($P < .001$). An ipsilateral PICC was successfully placed in 98% of Group A, compared to 32% of Group B ($P < .001$). After venogram, significantly more Doppler ultrasounds (DUS) were performed and thromboses diagnosed in Group B (57% and 36%) compared to Group A (21% and 8%) ($P < .003$; $P = .001$), respectively.

Conclusions: Previous catheter characteristics influenced the severity of venographic changes of CVS/O (Group B). Group B was associated with more subsequent symptomatic thromboses. This information may assist parents and referring physicians to anticipate potential adverse sequelae from CVS/O on the child's venous health.

ABBREVIATIONS

CThx = chylothorax, CVAD = central venous access device, CVS/O = central venous stenosis/obstruction, DUS = Doppler ultrasound, PICC = peripherally inserted central catheter, PTS = postthrombotic syndrome, SVC = superior vena cava

Central vein stenosis or occlusion (CVS/O), a complication of central venous access devices (CVADs), may compromise future venous access, and result in venous stasis (1–4). The CVS/O may occur from damage during CVAD insertion and from indwelling CVADs associated with turbulent flow, repetitive trauma, intimal hyperplasia, endothelial denudation, and adherent thrombi (5–7), and may be asymptomatic or symptomatic (eg edema of the ipsilateral extremity or the neck), and associated with thrombosis. The most prevalent risk factor for venous thromboembolism in children is a CVAD (80%) (4,8).

From Image Guided Therapy (R.G., R.C., A.A., J.D., J.A., D.P., B.C.), Diagnostic Imaging and the Department of Pediatrics, Division of Hematology/Oncology (N.W.), The Hospital for Sick Children, University of Toronto, 555 University Ave, Toronto, ON, M5G 1X8,Canada; Pediatric Interventional Radiology (R.G., L.R.B.), Department of Diagnostic Imaging, University Children's Hospital Zurich, Zurich, Switzerland; and the Swiss Childhood Cancer Registry (N.W.), Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. Received March 20, 2018; final revision received August 5, 2018; accepted August 20, 2018. **Address correspondence to:** R.G.; E-mail: ralph.gnannt@kispi.uzh.ch

R.G. receives grants from EMDO-Foundation (Zurich, Switzerland) and Helmut-Hartweg Funds (Bern, Switzerland). None of the other authors have identified a conflict of interest.

J Vasc Interv Radiol 2019; ■:1–9

https://doi.org/10.1016/j.jvir.2018.08.034

EDITORS' RESEARCH HIGHLIGHTS

- This study reviewed 100 pediatric venous access patients, those with venographically demonstrated central vein stenoses and occlusions, to determine how types of prior accesses affected stenosis development.
- Patients' median weight was 11 kg and median age was 2.7 years. They were split into stenoses and continuity to the superior vena cava vs no connection. The discontinuous group, ie those with more severe venous impact, were significantly associated with larger prior access devices (and more lumina); greater numbers of prior accesses; use of polyurethane catheters; and greater catheter malposition issues.
- Given the risks of worsening venous injuries and potential symptomatic or future access consequences, providers placing accesses should consider these risk factors, review prior ipsilateral venous imaging, and potentially counsel referrers and families accordingly.
- When planning the use and specific device selection of a central venous catheter in children, the risk of future venous compromise should be considered.

Venography during CVAD placement is not routine. In children, stenosis, occlusions, and venous collaterals are frequently observed on venograms performed during difficult peripherally inserted central venous catheter (PICC) placements (2). It is unclear what prior vascular access events lead to the development of CVS/O, eg types of CVADs, infections, or thromboses. It is also unclear what the clinical implications are for the child's future vessel health when CVS/O are found (eg future risk of thrombosis, postthrombotic syndrome, loss of central venous access) (9–11).

The purpose of this study was to analyze the preceding vascular access events (pre-venogram) and subsequent clinical impact (postvenogram) of CVS/O diagnosed in children. The hypothesis was that central venous stenosis/obstruction (CVS/O) in children is influenced by prior central venous access devices (CVADs), and is associated with future risk for thromboses.

MATERIAL AND METHODS

Study Design

This retrospective cohort study was conducted in a tertiary care-level pediatric teaching hospital. Institutional Research Ethics Board approval was obtained. The study cohort was identified from radiology reports on consecutive patients who had an abnormal contrast venogram during an image-guided (ultrasound, fluoroscopy) upper extremity PICC insertion in interventional radiology (IR), regardless of diagnosis, indication, or number of prior CVADs (Fig 1). The convenience target sample size was 100 abnormal venograms. Inclusion criteria were patients undergoing an upper extremity PICC placement, with abnormal venography showing deep venous stenosis or occlusion of the subclavian, brachiocephalic, or the superior vena cava (SVC), and/or opacification of venous collaterals. Patients were excluded if no venogram was performed, venogram was normal, images were not stored, or image quality was too poor to assess vessel patency. Only abnormalities of the central venous system were included. Abnormalities of the superficial and deep veins of the arm (brachial, cephalic, basilic veins) were excluded (Fig 1).

The search period started in January 2008, to ensure a sufficient sample size and to allow adequate follow-up for all patients. The target ($n = 100$) was reached in November 2012, providing minimum follow-up of 4 years (study terminated in 2016). The 100 patients were categorized into 2 groups by authors R.G. (radiologist with 9 years of experience) and R.C., (medical student, coauthor), with a review of 10 cases for consensus/audit purposes, by radiologist (B.C., 24 years of experience). Groupings were based on extent of the abnormalities seen on venography and divided into Group A and Group B, with the venographic changes more extensive in Group B:

Group A: Abnormal appearance (stenosis, wall irregularities, or occlusion) of the central veins (subclavian, brachiocephalic, or SVC), and visible venous collaterals, *with* an opacified connection to the SVC through the native vein or a collateral (Fig 2).

Group B: Abnormal appearance (stenosis, wall irregularities, or occlusion) of the central veins (subclavian, brachiocephalic, or SVC), and visible collaterals, but *without* any opacified connection to the SVC (Fig 3).

Results were organized and analyzed in 2 time frames: before and after venogram. Each patient's CVAD history, before and after venography, was examined, with follow-up (October 2016). A subanalysis was performed to examine the effect of age ($\leq$ 6 months and $>$ 6 months).

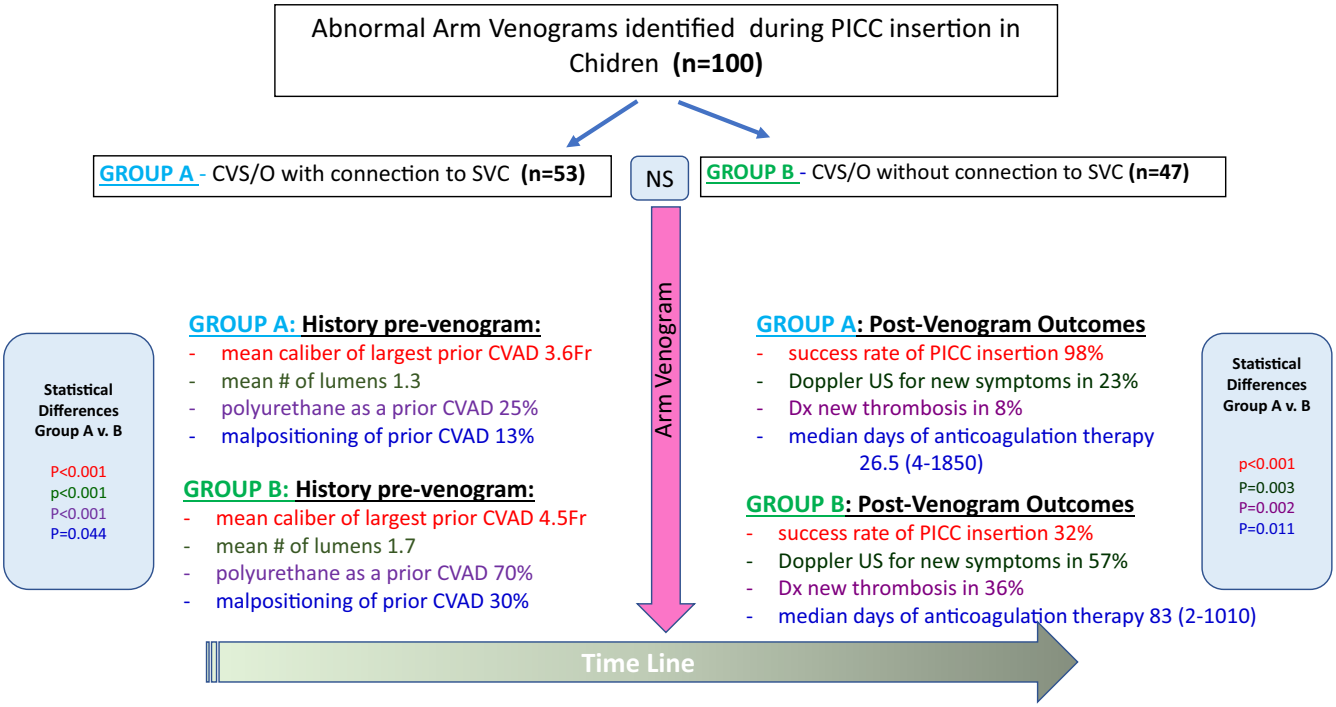
Data Collection

Data were collected from the Electronic Patient Charts, Vascular Access Database, the IR Database (Esh-IGT, www.esh.ca; Ontario, Canada), a hematology departmental database (Thrombosis), and PACS (GE, Milwaukee, Wisconsin). All feasible cross-referencing and confirmation techniques were employed between databases to ensure accuracy of the data.

To determine potential risk factors for developing CVS/O, the following were recorded:

Before venogram.—(*i*) Patient demographics at the time of the venogram; (*ii*) number, type, size and dwell times of all prior CVADs in the patient's history (including PICCs, central venous catheters, hemodialysis catheters, ports), number of venous Doppler ultrasounds (DUS) performed; number of thromboses diagnosed, and anticoagulation; (*iii*) most recent catheter in-situ prior to the venogram (called antecedent device), including the catheter material (silicone

Visual Synopsis



[CVS/O: central venous stenosis/obstruction; CVAD: central venous access device; NS: not significant]

or polyurethane), cuffed or uncuffed, side employed (left or right), vein used (basilic, brachial, subclavian, cephalic, internal jugular), indication for catheter (chemotherapy, antibiotics, total parenteral nutrition [TPN], medication, and/or fluids), and complications (thromboses, infection, malposition).

After venogram.—Success or failure of PICC placement during procedure with venogram, thromboses post-venogram (number of DUS examinations performed and thromboses diagnosed), anticoagulation and clinical sequelae from thrombosis (eg superior vena cava syndrome, post-thrombotic syndrome [PTS], chylothorax [CThx]). Prior cardiac surgery was recorded as a risk factor for developing above sequelae.

Definitions and Practice

Central veins included SVC, brachiocephalic, and subclavian veins. The deep veins included SVC, brachiocephalic, internal jugular, subclavian, and axillary. The superficial veins included the cephalic, basilic, and external jugular veins. Thromboses were diagnosed on venous DUS before and after venogram, and were defined using recognized sonographic criteria (12). A sonographically confirmed thrombus (occlusive or nonocclusive) was counted as 1 event; a subsequent thrombus found in a different vein was counted as a second event. Venous DUS assessment was performed on site, in clinically indicated symptomatic children (eg extremity swelling, pain, leaking at the CVAD site, or catheter malfunction suggestive of venous occlusion) or for follow-up of a known thrombosis. Routine DUS thrombosis surveillance screening was not performed. Catheter-related blood stream infections were laboratory proven. Catheter malpositions were based on radiographs.

Anticoagulation was defined as prophylactic (ie half of the treatment dose) or therapeutic (ie full treatment dose) based on recognized criteria using a variety of medications across all age groups (footnote, **Table 1**) (13). Prophylactic anticoagulation was administered only after CVAD insertion in patients with a history of a previous thrombosis and continued until removal of the CVAD. Therapeutic anticoagulation was administered following a documented deep venous thrombus, usually for 3 months, or longer if persistence of the thrombotic risk factor was demonstrated, as per international guidelines (13). Post-thrombotic syndrome was defined as per the modified Villalta score (mild, moderate, severe), a commonly used pediatric instrument for PTS detection (14) in the Thrombosis Clinic (15). Mild PTS corresponds to greater than 1 cm circumference differences with the contralateral arm and/or increased ipsilateral venous collaterals (14,15).

Venography

A venogram, including shoulder and upper chest area, was performed during PICC placement at the discretion of the interventionalist if difficulty was encountered advancing a guide wire or catheter centrally into the brachiocephalic vein and/or SVC. Contrast was hand-injected from the initial

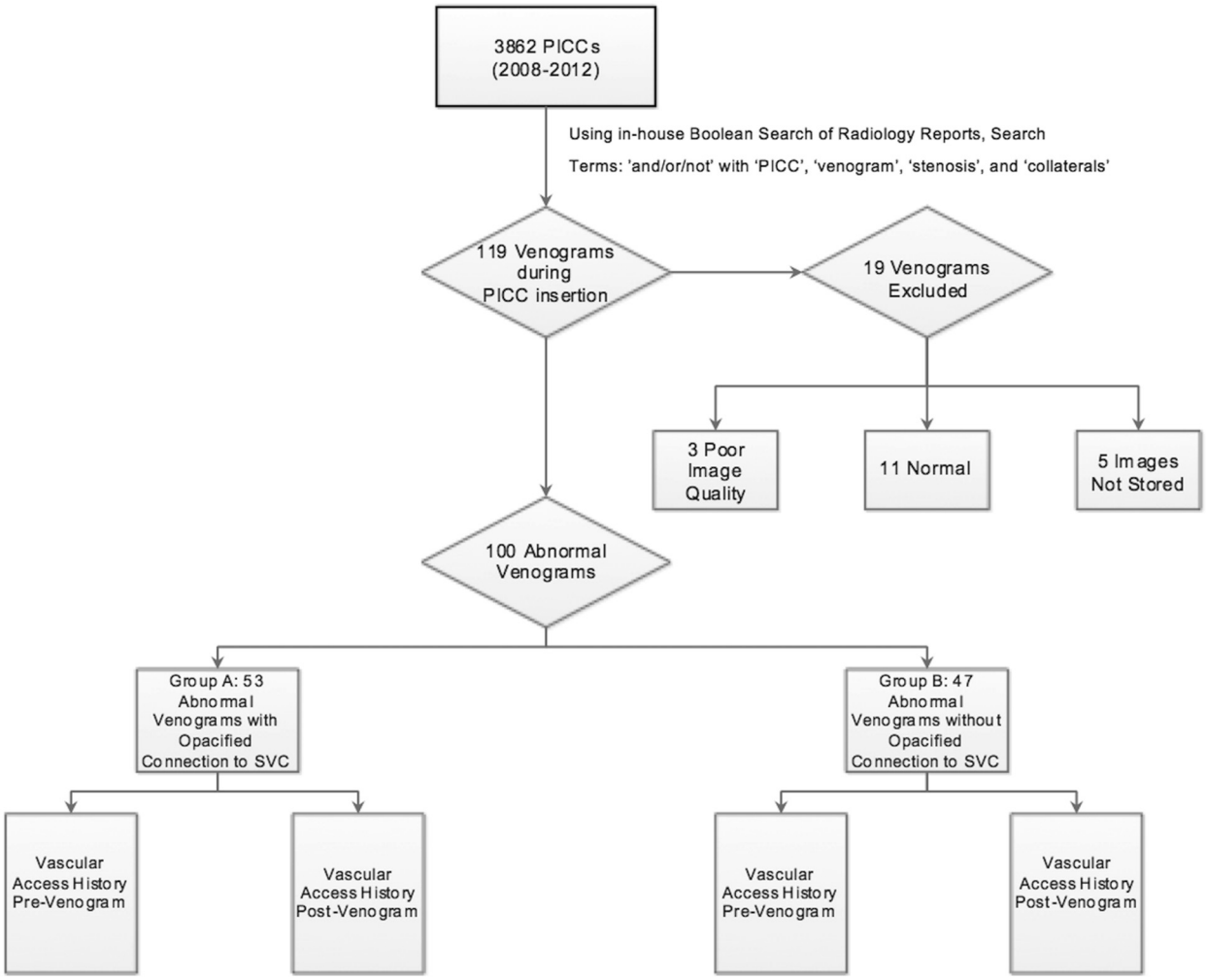


Figure 1. Flow chart of the patient cohort.

access site (basilic, cephalic, brachial, axillary vein) through a dilator, or through the nonadvanced PICC.

Patient Population

Of 3,862 PICCs placed in IR (2008 to 2012), 100 abnormal venograms were identified (Fig 1). There were 41 boys and 59 girls. The mean patient age was 2.7 years and mean weight was 11 kg (Table 2); the CVS/Os involved the right upper extremity in 94, and the left in 6. Fifty-three venograms were categorized into Group A and 47 venograms into Group B; 49 patients were $\leq$ 6 months old, and 51 were $>$ 6 months old. There was no statistical difference in age, weight, or gender between Groups A and B ($P > .05$).

Statistical Analysis

SPSS version 23.0 for Windows (SPSS Inc., Chicago, Illinois) was used. Frequency distributions and cross-tabulations of variables of interest were obtained. The Shapiro-Wilk test was used to assess normal distribution. Results were expressed as mean $\pm$ SD or median where appropriate. Student's *t*-test or Mann–Whitney U test was used for group comparisons for continuous variables. Chi-square or Fisher exact test was used to compare categorical variables. Differences were considered significant at $P < .05$ (2-tailed); those at $P > .05$ were not significant (NS).

RESULTS

Before Venogram

History of all CVADs before venogram.—The 100-patient cohort had received 437 prior CVADs, a median of 1.73 CVADs per patient (range 1–7). The mean cumulative dwell time of prior CVADs was 112 days (range 1–1,429 days). The differences between Groups A and B for number of CVADs and dwell time were not significant (Table 2). The mean size of CVADs before venogram was 4.1 French (range 1.9–10) and the number of lumens was 1.47 (range 1–2). There were significant differences between Group A and B in the patient's largest prior CVAD ($P < .001$) and the number of lumens ($P < .001$) (Table 2). Group B was almost 3 times more likely to have had an ipsilateral polyurethane catheter compared to Group A (relative risk [RR]: 2.86, CI: 1.72– 4.76, $P < .001$). The size of prior

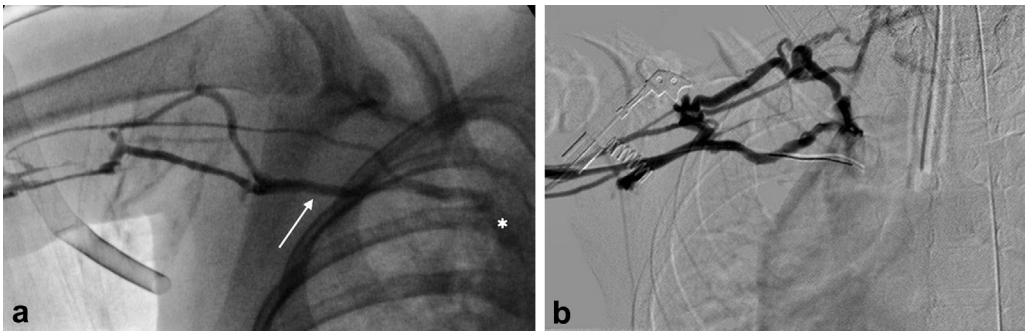


Figure 2. Example of venograms categorized as narrowing by the interventionalists (Group A). **(a)** a 7-year-old boy with 2 previous PICCs in the right arm. Vascular access was performed through the basilic vein. The venogram shows an abnormal appearance of the axillary/subclavian vein (arrow), but with a clear connection to the SVC (star). The PICC was placed without further issues on the ipsilateral arm. **(b)** A 5-year-old girl with 1 previous PICC in the right arm. Oblique view of DSA (digital subtraction angiography) from a brachial access shows 2 large draining veins; however, there is still a connection to the SVC. A PICC was placed through the lower branch; 0.014-inch wire perforated this branch without further complications.

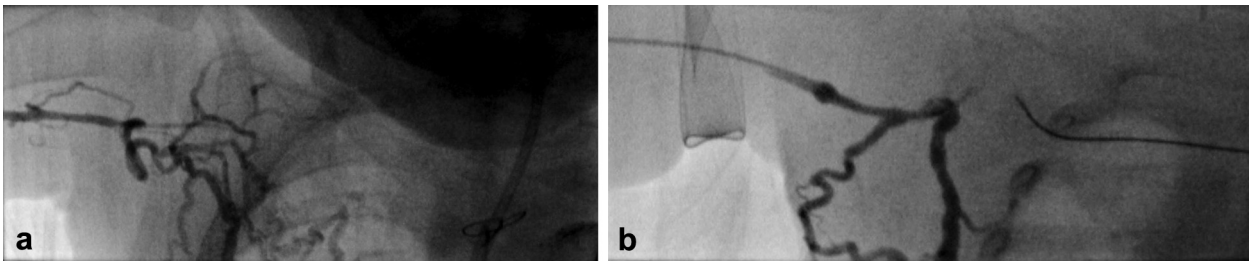


Figure 3. Examples of venograms categorized as occlusions by the interventionalists (Group B). **(a)** A 2-year-old boy with 2 previous PICCs and a temporary right jugular catheter. Vascular access was performed through the brachial vein. The venogram shows complete occlusion of the axillary/subclavian vein. Note: sternal wire from prior cardiac surgery. After several attempts to advance the wire into the SVC, the right arm was abandoned and the PICC was placed in the left arm. **(b)** A 3-year-old girl with 1 previous right arm PICC. Access was made through the basilic vein; venogram showed complete occlusion of the subclavian vein with large collaterals descending the right lateral chest wall.

CVADs, number of lumens, and dwell times were significantly greater in those $>$ 6 months old than $\leq$ 6months ($P = .026$, $P = .005$, $P = .027$, respectively).

The antecedent device before venogram.—The antecedent catheter before venogram showed no significant differences between Group A and Group B in use of cuffed or noncuffed catheters ($P = .13$), vein accessed ($P = .11$), indication for device: TPN ($P = .21$), antibiotics ($P = .85$), medication ($P = .81$), nor for device infection ($P = .42$) or blockage ($P = 0.75$). In Group B the antecedent catheter was more commonly of polyurethane material ($P < .001$) and malpositioned ($P = .04$) than Group A (Table 2). Both infection and malposition rates were higher than the institutional average for the relevant years (2008–2012; 6% and 8%, respectively).

Diagnosis of thromboses before venogram.—Seventy-five DUS on the ipsilateral arm/central veins had been performed to evaluate new symptoms in 46/100 patients, with 37 new thromboses diagnosed in 29/46 patients (Table 1). More DUS were performed and thromboses diagnosed in Group B than Group A, but differences were NS ($P = .073$ and $P = .137$, respectively).

Anticoagulation before venogram.—Six patients had been on prophylactic anticoagulation (2 in Group A, 4 in Group B), and 26 patients had been on therapeutic anticoagulation (12 in Group A, 14 in Group B) (Table 1). The median duration of prophylactic treatment in Group A was shorter than that of Group B, and median duration of therapeutic treatment was longer in Group A than in Group B, but the differences were nonsignificant (Table 1).

After Venogram

An ipsilateral PICC was successfully placed in 52/53 (98%) patients in Group A, compared to 15/47 (32%) in Group B ($P < .001$).

Diagnoses of thromboses after venogram.—Seventy-one ipsilateral DUS were performed in 38/100 patients due to the onset of new symptoms, and 33 new thrombi were diagnosed in 22/38 patients (Table 1). Group B patients were significantly more likely to require a DUS ($P = .003$; $\leq$ 6 months old, $P = .001$; $>$ 6 months old, $P = .007$) and have a new thrombosis ($P = .002$; $\leq$ 6 months old, $= .045$; $>$ 6 months old, $P = .001$) than Group A patients. Subset analysis of the 15 patients in Group B with a successful PICC showed 13 (89%) had ipsilateral DUS performed for new symptoms and new thromboses diagnosed in 8/13 (62%) patients (Fig 4). The differences in ipsilateral thromboses between Group A and

Table 1. Comparison of Frequency of Ultrasounds, Thromboses, and Anticoagulation Regimens before and after Venogram

Variable	Group A (n = 53) Group B (n = 47)	Before Venogram	After Venogram	*P* Value Comparing Pre- to Post- Venogram
# DUS for new symptoms [# of patients]	Group A	33 [22]	21 [11]	.202
	Group B	42 [24]	50 [27]	.243
	P value comparing Group A to Group B	$P = .073$	$P = .003$	
DUS binomial* (Yes/No)	Group A	22 (42%)	11 (23%)	.002
	Group B	24 (51%)	27 (57%)	.250
	P value comparing Group A to Group B	$P = .422$	$P < .0001$	
# New thromboses diagnosed [# of patients]	Group A	14 [12]	7 [4]	.002
	Group B	23 [17]	26 [17]	.250
	P value comparing Group A to Group B	$P = .137$	$P = .022$	
Thrombosis binomial* (Yes/No)	Group A	12 (23%)	4 (8%)	.202
	Group B	17 (36%)	17 (36%)	.389
	P value comparing Group A to Group B	$P = 0.185$	$P = 0.001$	
Median (range) # of days of prophylactic† anticoagulation [# of patients]	Group A	16 (8–24) [2]	118 (1–278) [4]	.225
	Group B	32 (3–65) [4]	123(19–228) [2]	.715
	P value comparing Group A to Group B	$P = 0.394$	$P = 0.368$	
Median (range) # of days of therapeutic‡ anticoagulation [# of patients]	Group A	75 (2–322) [12]	26.5 (4–1850 [12]	.460
	Group B	20.5 (3–538) [14]	83 (2–1010) [17]	.022
	P value comparing Group A to Group B	$P = .963$	$P = .011$	

Note–Anticoagulants included agents used to inhibit thrombin formation such as heparinoids (eg, unfractionated heparin [UFH/heparin], low molecular weight heparin [LMWH/enoxaparin/tinzaparin], oral vitamin K antagonist [warfarin], and direct thrombin inhibitors [argatroban]). In terms of dosing, anticoagulants were used in either therapeutic dose (ie full dose) or in prophylactic dose (ie corresponding to 50% of full dose) and titrated per kilogram body weight. No difference in agents used in children ≤ 6 months old or > 6 months old, except tinzaparin used in 2 children aged 4 and 7.5 years. Warfarin was used exclusively in children with cardiac surgical conduits/baffles to maintain patency with a mean age of 3.6 years (vs 1.5 to 1.7 for heparin and enoxaparin, respectively). Antiplatelet agents (aspirin) were used in 7 patients after cardiac surgery or liver transplantation to maintain patency of vessels, not for clot therapy.

DUS = Doppler ultrasound; # = number.

*Binomial (Yes or No) = all ultrasound / thromboses are counted as 1 per patient, irrespective of number per patient.

†Prophylactic anticoagulation agents – heparin or enoxaparin used.

‡Therapeutic anticoagulation agents – heparin, enoxaparin, tinzaparin, or warfarin. Rarely, argatroban.

B with a successful PICC were highly significant (chi-square = 16.49; $P < .0001$).

Anticoagulation after venogram.—After venogram, 6/100 patients received prophylactic anticoagulation (4 in Group A; 2 in Group B), and 29/100 patients required therapeutic anticoagulation (12 in Group A; 17 in Group B). The median duration of therapeutic anticoagulation was significantly longer in Group B patients ($P = .011$); the differences in prophylaxis duration were nonsignificant ($P = .368$).

Clinical sequelae after venogram.—The Hematology/Thrombosis Team monitored 38 patients for 51 new thromboses, including 12/38 monitored both before and after venogram (1 was followed up elsewhere). Six of the 38 patients (15%) patients were diagnosed with PTS (2 in Group A; 4 in Group B), 8/38 (21%) with CThx (1 in Group A; 7 in Group B), and 2/38 (5%) with SVC syndrome (1 in Group A and 1 in Group B). An underlying cardiac diagnosis was noted in 20/38 patients. Postthrombotic syndrome and CThx occurred more commonly in those with underlying cardiac disease (4/20 [20%] and 7/20 [35%]), respectively, compared to those without cardiac pathology (2/18 [11%] and 1/18 [5.6%]), respectively (difference marginally significant, $P = 0.056$). Superior vena cava syndrome was similarly distributed between patients with and without an underlying cardiac disease (1/20 [5%], 1/18 [5.6%]).

DISCUSSION

Awareness of vessel health in children and preserving their venous access sites is a key responsibility of the pediatric interventional radiologist, especially in children with complex comorbidities who face long-term or even lifelong vascular access needs (9–11). The pediatric interventionalist may achieve this by simple measures, eg, ensuring a good indication for every inserted CVAD, reviewing prior imaging, placing the smallest size and fewest lumens to serve the child's needs, placing the CVAD tip centrally, and changing access sites only when necessary.

Table 2. Clinical and Line Characteristics before Venogram

All Lines	Group A (n = 53)	Group B (n = 47)	*P* Value
Age, y, mean (median, range)	2.9 (0.5; 0.04–17.3)	2.6 (0.5; 0.05–17.9)	.73
Weight, kg, mean (median, range)	11.9 (4.45; 0.68–69.3)	10.3 (4.75; 0–66)	.71
Gender, male / female	21 / 32	20 / 27	.97
Devices before venogram, n, mean	1.8	1.7	.82
French size of largest line before venogram, mean	3.6	4.5	<.001
Lumens of lines placed before venogram, mean	1.3	1.7	<.001
Dwell time, d, mean	111.3	112.6	.113
Details of Antecedent Line before Venogram			
Material, silicone / polyurethane, n	40 /13	14/33	<.001
Vein used for CVAD prior to venogram, IJV/SV/ DV, n	7 / 34 / 12	8 / 18 / 21	.11
Line cuffed, n	43	32	.13
Usage of line prior to venogram, n			
•TPN	21	13	.21
•Antibiotics	19	16	.85
•Medication	13	18	.81
Infection, n	11	13	.42
Malposition,* n	7	14	.04
Blockage, n	6	4	.75

DV = deep vein; IJV = internal jugular vein; SV = superficial vein; TPN = total parenteral nutrition.
*Malposition: Common malpositions include: (*i*) central tip flipping into the contralateral brachiocephalic vein or jugular vein; (*ii*) tip ascending high with patient growth, into the SVC or inominate, and (*iii*) descending low into the right atrium.

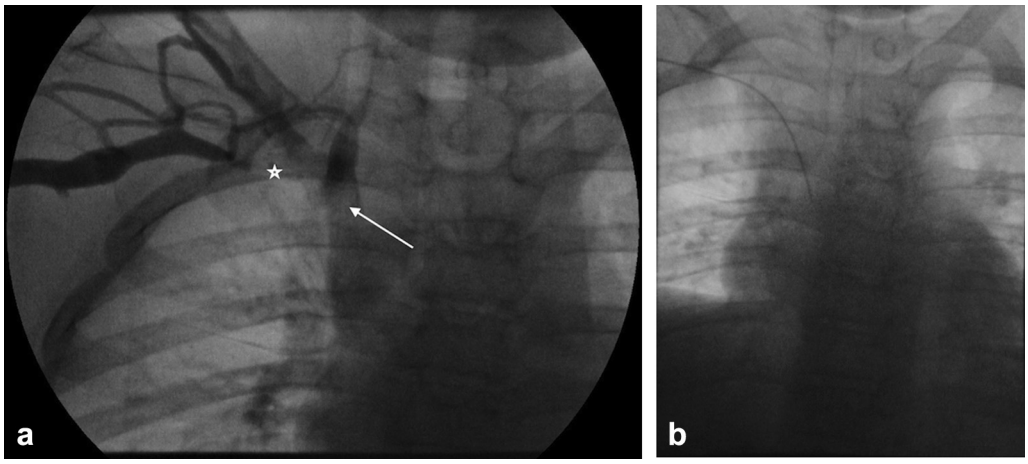


Figure 4. Venogram from a right arm vein in an 8-year-old female with prior PICC placed in the right arm. The native axillary vein is opacified, but with complete occlusion of the subclavian vein (star). Opacification of the SVC (arrow) through collaterals is seen. Ultimately, a PICC was successfully placed through the occluded subclavian vein. Patient had an ultrasound due to severe swelling of the right arm at Day 2, and at Day 5 after PICC insertion, a thrombus was seen in the right axillary vein.

Central venous stenosis/obstruction is clinically important, affecting blood return to the heart. In severe cases, the entire upper venous system is compromised. This study explored a select group of children diagnosed with CVS/O, to evaluate factors associated with the development of CVS/O, as well as the sequelae of CVS/O. The cohort was associated with a higher incidence of previous infection and malposition than the institutional average. Patients in Group B had larger diameter, more lumens, malpositions and use of polyurethane catheters in their prior CVADs than those in Group A. Successful PICC placement was significantly less frequent in Group B, with greater likelihood of subsequent symptoms (need for DUS, diagnosis of thromboses and therapeutic anticoagulation).

The success rate for PICC placement in the ipsilateral arm with CVS/O (68% overall, Groups A and B combined) was lower than in an adult cohort studied by Park et al (86%) (16). A lower success rate was not unexpected because it included young children (mean age 2.7 years, mean weight 11 kg) compared to adults. Stenosis in preexisting small veins would more likely prevent successful passage of a new PICC. The impact of these stenoses was seen in the

numbers of patients who became symptomatic and required a DUS post PICC, indirectly indicating the critical nature of the stenosis with development of stasis/congestion symptoms in the presence of a new space occupying PICC.

The incidence of CVS/O after PICC or Port-a-cath insertion has been reported to be approximately 7% (10). In the same period of this study (2008–2012), 3,862 PICCs were placed in this institution. Identification of only 100 abnormal venograms is therefore low (approximately 2.6%). More than half the cohort (54%) had never undergone a prior DUS, ie they were asymptomatic, and CVS/O became apparent only during the difficult PICC insertion, suggesting CVS/O is frequently silent. Conversely, not all symptomatic children were found to have associated thromboses on DUS. The cohort did not account for others who may have had CVS/O or thrombosis, but who did not undergo a subsequent PICC or venography, and remained undetected. The incidence of PICC-associated peripheral thromboses detected by screening ultrasound in adults is much higher (72%)(17). The 100 children studied therefore represent the tip of an iceberg. The division into 2 groups, based on the extent of venographic abnormalities, show clinically relevant differences in severity of CVS/O between both groups (requirement for ultrasound, success of ipsilateral PICCs, diagnoses of thrombosis, and clinical sequelae), with Group B more symptomatic than A, before and after venogram.

The mechanism for forming CVS/O is not always known. Potential contributors are vessel wall damage at the time of insertion, indwelling catheters causing continuous endothelial damage, intimal hyperplasia, turbulent flow, and thrombosis (5,18). The preponderance on the right side reflected the institutional practice of using the right arm as first option for CVAD placement. The significant difference in catheter size and number of lumens between Group A and B potentially contributed to CVS/O. The relative size of vein to catheter is important because the vein diameter is small in infants. Although no measurement of the diameters of the veins were taken, vein sizes were likely similar because there was no significant difference in the ages and weights of patients in Groups A or B. The mean age (2.7 years) and weight (11 kg) of the cohort are younger and smaller than the institutional average of patients undergoing a PICC (4.5 years; 18 kg), suggesting that CVS/O might be more common in smaller children. Whether $\leq$6 months old or $>$6 months old, Group B patients required more DUS and were diagnosed with more thromboses after venogram than Group A. However, differences in variables such as dwell times, largest diameter, and number of lumens of prior CVADs were more significant in those $>$6 months than $\leq$6 months in Group B patients than Group A patients.

Endothelial damage during catheter insertion may contribute to CVS/O. Inserting a double lumen PICC over a single wire results in an eccentric wire, and the vessel wall is prone to damage from the blunt tip of the catheter. In this cohort, 43% double lumen CVADs (188/437) had been placed, whereas the institutional average in the same timeframe was 21% (819/3862). Vein injury also may occur from the catheter lying in contact with the vessel wall. Arm movement, breathing, and cardiac cycles cause catheter movement with friction on the endothelium (19). Even short-term catheters can be associated with focal intimal injury and thrombus formation (18). Significantly more polyurethane catheters were used in Group B compared to Group A, suggesting catheter material is important (20). Although polyurethane softens at body temperature, polyurethane is a stiffer material than silicone. Surface irregularities on polyurethane devices make them more susceptible to thrombus adhesion (21, 22).

This study has several limitations. A convenience sample was a chosen as a representative subgroup, but actual incidences may vary if a large prospective study is undertaken. The search terms may have overlooked or missed some cases. This study was not designed to determine causation for CVS/O. Prospective studies designed differently would be required to determine causality and validate findings of this study. A strength of this study was the creation of a select cohort of patients with documented abnormal venography. Division into 2 groups was based on venographic patterns, which are prone to assignment error and inherent variability in venographic technique. Venographic image quality varied, depending on the contrast volume injected, which was usually small, and use of fluoroscopy or digital subtraction angiography. More precise characterization of the venographic abnormalities seen on venogram (eg assigning percentage stenosis, enumerating collaterals) would be inaccurate, due to such technical inconsistencies. Classification was based on an opacified venous connection to the SVC, regardless of whether it was a collateral or native vein. Park et al (16) classified CVS/O and collaterals into 3 groups, depending on distribution and degree of venous collaterals identified on venogram. The rationale behind the classification used here was that symptoms (congestion, swelling, pain) are less likely if there is any route for adequate venous drainage of the limb (ie connection to SVC, Group A). The duration of CVS/O changes (acute or long-standing) could not be determined. Prior catheter insertions were assumed not to be difficult (as no venogram had been performed). No measurement of vein sizes was available, so correlation with PICC French size was not done. No clinical comparisons were made between both groups in Hematology/Thrombosis follow-up clinics. Prophylactic anticoagulation may have been underreported.

In conclusion, the findings indicate that previous catheter characteristics (material, size, number of lumens, malposition) influence the severity of CVS/O. Detection of CVS/O on venography is associated with subsequent symptoms, with or without thromboses requiring anticoagulation. Many CVS/Os remain undiagnosed. It is debatable if a PICC should be placed ipsilaterally to CVS/O if there is no visible venous SVC connection, as thromboses are significantly more likely to occur. Adverse outcomes of PTS, SVC syndrome, and CThx are more

likely to occur in those with concomitant cardiac pathology (marginally significant). It behooves the interventionalist to review available images while planning a PICC. This study provides important information for the pediatric interventionalist to share with parents and referring physicians, to anticipate potential adverse sequelae in the child's future venous health.

ACKNOWLEDGMENTS

We thank the IGT team at The Hospital for Sick Children for assisting with recording and labeling of all the images that were used for our data analysis.

REFERENCES

1. Ters El M, Schears GJ, Taler SJ, et al. Association between prior peripherally inserted central catheters and lack of functioning arteriovenous fistulas: a case-control study in hemodialysis patients. Am J Kidney Dis 2012; 60:601–608.
2. Yang RY, Moineddin R, Filipescu D, et al. Increased complexity and complications associated with multiple peripherally inserted central catheter insertions in children: the tip of the iceberg. J Vasc Interv Radiol 2012; 23:351–357.
3. Shin HS, Towbin AJ, Zhang B, et al. Venous thrombosis and stenosis after peripherally inserted central catheter placement in children. Pediatr Radiol 2017; 27:556.
4. Jaffray J, Bauman M, Massicotte P. The impact of central venous catheters on pediatric venous thromboembolism. Front Pediatr 2017; 5:5.
5. Agarwal AK, Patel BM, Haddad NJ. Central vein stenosis: a nephrologist's perspective. Semin Dial 2007; 20:53–62.
6. Wessler S. Thrombosis in the presence of vascular stasis. Am J Med 1962; 33:648–666.
7. Stein PD, Sabbah HN. Measured turbulence and its effect on thrombus formation. Circ Res 1974; 35:608–614.
8. Monagle P, Adams M, Mahoney M, et al. Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry. Pediatr Res 2000; 47:763–766.
9. Moureau NL, Trick N, Nifong T, et al. Vessel health and preservation (Part 1): a new evidence-based approach to vascular access selection and management. J Vasc Access 2012; 13:351–356.
10. Hallam C, Weston V, Denton A, et al. Development of the UK Vessel Health and Preservation (VHP) framework: a multi-organisational collaborative. J Infect Prev 2016; 17:65–72.
11. Ventura R. Liverpool: Aintree University Hospital NHS Foundation …, 2016 (3AD) Implementing a Vessel Health & Preservation Programme. Available at: http://www.3mlearning.co.uk/media/1117/roy-ventura-vessel-health-programme-may-2016.pdf.
12. Prandoni P, Polistena P, Bernardi E, et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. Arch Intern Med 1997; 157:57–62.
13. Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e737S–e801S.
14. Kuhle S, Koloshuk B, Marzinotto V, et al. A cross-sectional study evaluating post-thrombotic syndrome in children. Thromb Res 2003; 111:227–233.
15. Avila ML, Brandão LR, Williams S, et al. Pediatric post-thrombotic syndrome in children: Toward the development of a new diagnostic and evaluative measurement tool. Thromb Res 2016; 144:184–191.
16. Park KB, Choo SW, Do YS, et al. Peripherally inserted central catheter placement in patients with unsuspected central venous obstruction. J Vasc Interv Radiol 2008; 19:552–556.
17. Itkin M, Mondshein JI, Stavropoulos SW, et al. Peripherally inserted central catheter thrombosis–reverse tapered versus nontapered catheters: a randomized controlled study. J Vasc Interv Radiol 2014; 25:85–91.e1.
18. Forauer AR, Theoharis C. Histologic changes in the human vein wall adjacent to indwelling central venous catheters. J Vasc Interv Radiol 2003; 14:1163–1168.
19. Connolly B, Amaral J, Walsh S, et al. Influence of arm movement on central tip location of peripherally inserted central catheters (PICCs). Pediatr Radiol 2006; 36:845–850.
20. Gnannt R, Waespe N, Temple M, et al. Increased risk of symptomatic upper-extremity venous thrombosis with multiple peripherally inserted central catheter insertions in pediatric patients. Pediatr Radiol 2018; 48:1013–1020.
21. Thomsen HK, Kjeldsen K, Hansen JF. Thrombogenic properties of arterial catheters: a scanning electron microscopic examination of the surface structure. Cathet Cardiovasc Diagn 1997; 3:351–358.
22. Bourassa MG, Cantin M, Sandborn EB, Pederson E. Scanning electron microscopy of surface irregularities and thrombogenesis of polyurethane and polyethylene coronary catheters. Circulation 1976; 53:992–996.